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Myopericarditis following mRNA COVID-19 Vaccination in Adolescents 12 through 18 Years of Age

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Data Availability Statement: The de-identified data associated with this study is summarized in the Table. Additional data will be made available upon request.

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Objectives: To characterize the clinical course and outcomes of children who developed probable myopericarditis after vaccination with the Pfizer- BioNTech (BNT162b2) COVID-19 mRNA vaccine.

Study design: A cross-sectional study of 32 children, aged 12 through 18 years, diagnosed with probable myopericarditis following COVID-19 mRNA vaccination as per the CDC criteria for myopericarditis at 9 US centers between May 10, 2021 and June 20, 2021. We retrospectively collected the following data: demographics, SARS-CoV-2 virus detection or serologic testing, clinical manifestations, laboratory test results, imaging study results, treatment and time to resolutions of symptoms.

Results: Most (90%) cases followed the second dose of vaccine, and chest pain (100%) was the most common presenting symptom. Patients came to medical attention a median of 2 days (range: <1-20 days) after receipt of Pfizer mRNA COVID-19 vaccination. All adolescents had an elevated plasma troponin concentration. Echocardiographic abnormalities were infrequent, and 84% showed normal cardiac function at presentation. However, cardiac magnetic resonance imaging (CMR), obtained in 16 patients (50%), revealed that 15 (94%) had late gadolinium enhancement consistent with myopericarditis. Most were treated with ibuprofen or an equivalent NSAID for symptomatic relief, one patient was treated primarily with a corticosteroid orally and three patients were given a corticosteroid orally after initial administration of ibuprofen or NSAID; two patients also received intravenous immune globulin. Symptom resolution was observed within 7 days in all patients.

Conclusions: Our data suggest that symptoms due to myopericarditis following mRNA COVID-19 vaccination tend to be mild and transient. Approximately one half of patients underwent CMR, which revealed evidence of myocardial inflammation despite a lack of echocardiographic abnormalities.

The US Food and Drug Administration (FDA) issued Emergency Use Authorization (EUA) on December 11, 2020 for the Pfizer-BioNTech mRNA COVID-19 Vaccine (BNT162b2, Pfizer-BionTech, Pfizer, Inc; Philadelphia, Pennsylvania) in individuals 16 years of age and older.[1] On May 10, 2021, the FDA expanded the EUA of the same vaccine to children 12 through 15 years of age.[2] The Centers for Disease Control and Prevention (CDC) subsequently recommended the COVID-19 vaccine for children 12 years and older via a notification issued on May 12, 2021. As of June 26, 2021, 322 million doses of various COVID-19 vaccines have been administered, of which 4,521,732 children aged 12 through 15 years (5% of the US population) and 3,213,339 adolescents aged 16 and 17 years (2.5% of US population) had received at least one dose of the Pfizer-BioNTech COVID-19 vaccine.[3] Since April 2021, an increase in myopericarditis has been reported temporally associated with COVID-19 vaccination, particularly among adolescents. The American Academy of Pediatrics (AAP) and the American Heart Association (AHA) have endorsed CDC recommendations and reiterated the potential benefits of COVID-19 vaccination, which outweigh the apparent small risk of myopericarditis in children 12 years of age and older.[4-5] We summarize our findings in 32 adolescents 12 through 18 years of age with vaccine-associated myopericarditis from 9 centers across the US.

Methods

A multi-institutional group of pediatric cardiologists, pediatric intensivists, and pediatric infectious disease physicians from 9 centers across the United States pooled their data for this retrospective case series. Children were included in the study if they presented with probable myopericarditis after mRNA COVID-19 vaccination between May 10, 2021 and June 20, 2021 and were aged 12 through 18 years. Clinical and laboratory data were collected free of personal identifiers except for age, race, and sex— and submitted by collaborating authors via secure email.

We collected the data retrospectively according to the institutional review board policies of each of the participating institutions.

Patient data included age, sex, race and ethnicity, history or evidence of prior SARS-CoV-2 infection (ie, either rapid COVID-19 test or PCR for SARS-CoV-2), and symptoms at presentation (i.e., chest pain, fever, shortness of breath, fatigue, nausea, vomiting, abdominal pain, or any other unusual symptoms). The laboratory data included testing to detect other viral causes of myocarditis, serum concentrations of an inflammatory marker (C-reactive protein) and cardiac biomarker (troponin), electrocardiographic findings, echocardiographic findings, and cardiac magnetic resonance imaging (CMR) findings. Results of serologic testing for SARS-CoV-2 antibodies as performed at the discretion of, and using tests available to, the reporting sites were collected. Additional data included the duration of hospitalization and details of the therapy administered.

Results

The Table summarizes the characteristics of 32 adolescents, 12 through 18 years of age, who had probable myopericarditis as per the CDC defined criteria for diagnosis of myocarditis and pericarditis.[6] Twenty-eight (87.5%) were males, and 29 (90 %) presented after the second dose of the mRNA COVID-19 vaccine. Three adolescents (~10%) (Patients 4, 8, and 27) had probable myopericarditis after the first dose. One of these patients (Patient 4) had evidence of probable myopericarditis 20 days after the first dose, with complete clinical resolution. He again presented with chest pain and was diagnosed with probable myopericarditis 1 day after the second dose of the vaccine.

The most common presenting symptom was chest pain. A few patients had additional symptoms, including fever, shortness of breath, fatigue, nausea, vomiting, and abdominal pain (Table). After the second dose of vaccine, 72% and 86% of patients reported onset of symptoms

within 2 and 3 days, respectively (median 2 days, range <1- 4 days). Time to onset of symptoms following a first dose of vaccine in 3 patients (patients 4, 8, 27) was 20, 3 and 5 days, respectively. All 32 patients had elevated plasma troponin concentration (Figure 2). Serum CRP concentration was measured in 24 patients (75%) and was elevated in all except two (Patients 27 and 32).

Only one adolescent (patient 8) in the series had a prior history of symptomatic COVID-19 infection (4 months prior to presentation) but COVID antibody test was negative at presentation with myopericarditis. COVID-19 anti-nucleocapsid antibody testing was performed in 22 patients; only 4 tests (patients 5, 6, 9, and 25) which were positive. SARS-CoV-2 anti-spike protein IgG antibody enzyme immunoassay (EIA) was performed in 14 patients (all presenting after the second dose) and all tests were positive. One patient (Patients 4 and 5 [Table]), had myopericarditis after both the doses of mRNA COVID-19 vaccine. Antibody testing was not performed after the first episode of myocarditis. He tested positive for COVID-19 anti-nucleocapsid antibody after the second episode. COVID-19 anti-spike antibody testing was not performed on this patient. COVID-19 RT-PCR was performed on respiratory tract specimens in 89 % of patients at presentation and was negative in all except one patient (Patient 30). Viral respiratory panel was negative in 22 patients tested (69%). One adolescent had positive serum parvovirus B-19 IgM antibody (Patient 27).

Electrocardiographic (ECG) abnormalities were common (88%). Abnormal ECG findings included ST-segment elevation (66%), isolated nonspecific ST changes (19%), ST-segment depression (3%) and PR-segment depression (9%). Three patients (Patients 5, 8, and 26) had asymptomatic non-sustained ventricular tachycardia (Figure 1; available at www.jpeds.com), one had asymptomatic non-sustained supraventricular tachycardia (Patient 30); additionally, one patient (Patient 3) was noted to have frequent premature ventricular contractions on telemetry during hospitalization.

Echocardiography was performed in all patients and showed normal left ventricular systolic function in the majority (27 patients, 84%). Five patients (Patients 1, 16, 17, 19, and 27) had mildly diminished ventricular function with abnormal left ventricular ejection fractions (LV EFs) ranging from 48% to 52% (Figure 2). A few patients were noted to have trivial or small amount of pericardial fluid; none of the patients had a substantial pericardial effusion. In contrast, CMR, which was performed in 16 of 32 patients (50%), revealed late gadolinium enhancement (LGE) in 15 (94%) (Figure 3). The pattern of enhancement was subepicardial in 5 (33%), subepicardial and mid-myocardial in 6 (40%), mid-myocardial and sub endocardial in 1 (7%), mid-myocardial in 2 (14%), and transmural in 1 (7%) patient. Additional findings included myocardial edema on T2 mapping in 6 (37.5%) and a small pericardial effusion in 3 (19%) patients, one of whom did not have LGE.

Hospitalized patients had stays of 2-7 days (median 3 days). All recovered clinically and were discharged home in less than 7 days. Three patients (Patients 4, 10 and 32) did not require hospitalization and were followed as outpatients. Most patients were treated with ibuprofen or an equivalent NSAID and responded well; one was treated primarily with a corticosteroid orally, three with a corticosteroid after initial ibuprofen or NSAID administration due to rising troponin concentration; two (Patients 5 and 31) also received intravenous immune globulin in addition to other therapies, which was based on physician and family preference than specific clinical criteria. All afflicted adolescents made a complete clinical recovery in 1 week and were doing well at the most recent follow up.

Discussion

Our report represents a large series of adolescents with myopericarditis following mRNA COVID-19 vaccination.[6-7] The US Food and Drug Administration added a warning about the risk of myocarditis and pericarditis to the fact sheet of both mRNA vaccines on June 25, 2021.[8] Our

findings suggest that, in many instances, myopericarditis following mRNA COVID-19 vaccination tends to be mild and resolves within a few days. Elevation of plasma troponin concentration and abnormalities on CMR are common in these patients; however, overt abnormalities on echocardiography are unusual and mild if present. Furthermore, given the large number of doses mRNA COVID-19 vaccine administered to adolescents at this writing, this newly recognized complication is very infrequent, and benefits of vaccination outweigh the risk of vaccination for adolescents 12 years of age or older. Careful observation for reporting of myopericarditis after second doses of vaccine is warranted especially in 12- through 15-year-olds as at the time of this writing, less than 6 weeks after the recommendation, relatively few of the approximately 4.5 million doses administered would be expected to have been second doses.

Thus far, 79 children aged 16 or 17 years, and 196 young adults aged 18 through 24 years have been confirmed by CDC as having myocarditis/pericarditis following mRNA COVID-19 vaccination after analyzing VAERS data; many more cases are under review currently.[9] The preliminary estimated risk of myocarditis following administration of the Pfizer-BioNTech COVID-19 mRNA vaccine is 1.2 and 10.4 per million after administration of the first and second dose, respectively among those 16 through 39 years of age.[10] In a report from the Israeli Ministry of Health, one in 3000 to one in 6000 men aged 16 through 24 years who received the mRNA COVID-19 vaccine developed myocarditis/pericarditis.[11] Ninety percent of affected individuals in Israel were young men. Although the background rate of myocarditis in this population is high, the rate following vaccination appeared to be 5- 25 times higher than the background rate.[11] European Medicines Agency also has reported myocarditis/ pericarditis related to mRNA vaccination but concluded no indication of a causal relation with the vaccine.[12] The striking male preponderance in our cohort is consistent with reports in young adults and small series of adolescents.[6, 11]

A similar increase in myocarditis/pericarditis has not been reported following administration of non-mRNA COVID-19 vaccines, such as Janssen Vaccine (Ad.26.COV2.S) (Johnson & Johnson; New Brunswick, New Jersey). Continuing reports following administration of mRNA platform-based vaccines suggest a unique risk and several mechanisms have been hypothesized. It has been speculated from data reported in the initial trials of mRNA vaccine in adults [13-14] that mRNA vaccines might generate a very high antibody response in a small subset of young people, thus eliciting a response similar to multisystem inflammatory syndrome in children (MIS-C) associated with SARS-CoV-2. However, anti-spike IgG antibody titers in a small subset of our patients, were variable (data not shown) and did not correlate with the extent of cardiac injury. Furthermore, Muthukumar et al[15] conducted detailed immunologic investigation in a 52-year-old man who developed myocarditis three days after receiving the second dose of Moderna mRNA COVID-19 vaccine and found that his antibody responses to 18 different SARS-CoV-2 antigens did not differ from (and were lower for some antigens) vaccinated controls who did not develop complications. Other hypothesized mechanisms include induction of anti-idiotype cross-reactive antibody-mediated cytokine expression in the myocardium, leading to aberrant apoptosis, resulting in inflammation of the myocardium and pericardium.[16] Induction of a nonspecific innate inflammatory response by the mRNA vaccine or a molecular mimicry mechanism between viral spike protein and an unknown cardiac protein also has been postulated.[17] The mRNA in the vaccine is a potent immunogen and produces bystander or adjuvant effects by cytokine activation of pre-existing autoreactive immune cells.[18]

The complication of mRNA vaccine-related myopericarditis has predominantly been reported in males. Whether hormonal or other differences play a role in expression of this disease has not been evaluated systematically.

The definitive diagnosis of myocarditis is established by histologic criteria, including acute myocyte injury with inflammatory cell infiltration, especially lymphocytes.[19] In most patients, myocarditis is transient and self-limited; therefore, endomyocardial biopsy is not justified. Elevated serum troponin concentration may indicate acute cardiac injury but is neither sensitive nor specific for the diagnosis of myocarditis. Because of variable clinical manifestations of myocarditis, it is helpful to follow the CDC definition of acute myocarditis and acute pericarditis. As demonstrated by our data, cardiac magnetic resonance (CMR) imaging with tissue characterization using T1 and T2 mapping is a useful noninvasive modality for diagnosing mRNA COVID-19 vaccine-associated myocarditis/pericarditis, especially in patients with normal echocardiographic findings.[20]

Treatment considerations for non-vaccine-associated myocarditis include anti-inflammatory medications and guideline-directed medical therapy if left ventricular function is diminished.[21] There are no systematic data on specific treatment of COVID-19 vaccine-associated myocarditis. As shown in our study, ibuprofen or equivalent nonsteroidal anti-inflammatory drugs (NSAIDs) seem to provide a beneficial response and could be prudent initial management. The role of corticosteroids and IVIG remains unclear, but these agents could reduce the immune response triggered by the vaccine and have a role in NSAID- unresponsive patients.

There are several limitations to our study. We do not have the data on the total number of children vaccinated during the study period; therefore, the incidence of COVID-19 mRNA vaccine-associated myocarditis/pericarditis cannot be determined. Moreover, although the patients who were symptomatic and sought medical care were evaluated and diagnosed, several COVID-19 vaccine-associated myocarditis episodes could be subclinical or have trivial symptoms that did not lead to seeking medical care. Reported cases could underestimate the true incidence of mRNA COVID-19 vaccine-associated myocarditis/pericarditis. As the Pfizer-BioNTech (BNT162b2) vaccine is the only mRNA vaccine currently approved in individuals at 12 through 15 years of age, we have presumed that all patients received this vaccine (without verifying vaccination cards). Not all laboratory tests, including testing for other causes of viral myocarditis, serologic testing for COVID-19, and CMR, were available for each patient due to variability in practice among individual physicians and centers. The typical occurrence of non-COVID vaccine-associated myocarditis in children and adolescents is approximately 10-20/100,000 annually.[22] After the initiation of COVID-19 vaccination and relaxation of restrictions, there has been an increase in overall mobility after a prolonged period of lock-down. Therefore, there might have been an increase in non-mRNA COVID-19 vaccine-associated myocarditis of undetermined viral cause, which could have been misdiagnosed as COVID-19 vaccine-associated myocarditis.

The long-term impact of myopericardial inflammation following COVID-19 mRNA vaccine, especially in those with extensive myocardial involvement on CMR, remains unknown and needs to be systematically evaluated. Further studies are required to elucidate the pathophysiology that underlies this complication to seek mitigation strategies and to delineate optimal therapy.

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Study concept and design: BD, UK, PR DC, SP, and DK

Acquisition, analysis, or interpretation of data: BD, UK, DC, SP, BP, CM, HHN, CDC, IGR, BA, BJF, NE, and DK

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Critical revision of the manuscript: BD, UK, PR, DC, SP, BP, CM, HHN, GG, TH, AT, CK, SA, CD, SH, KS, CM, NRC, BP, JYA, BA, JS, KAB, CDC, BMG, IEGR, GK, OS, MW, NE, BJF and DK.

Conflict of Interest Disclosures: No financial conflict of interest is reported.

Table and Figure Legends

Table 1. Characteristics of 32 Adolescents with Probable Myopericarditis Following mRNA COVID-19 Vaccine Administration.

C, Caucasian; AA, African American; H, Hispanic; A, Asian; O, Others; ECG, Electrocardiogram; ECHO, Echocardiography; CMR, Cardiac magnetic resonance; M, Male; F, Female; ND: Not done; NL, Normal; LV, Left ventricle; Fx, Function; LGE, Late gadolinium enhancement; NS VT, Non-sustained ventricular tachycardia; SVT, Supraventricular tachycardia; Rx, Treatment; CRP, C-Reactive protein; Tn, Serum troponin concentration; PE, Pericardial effusion.

Figure 1; online only. Non-sustained ventricular tachycardia noted in Patients 5 and 8.

Figure 2. Common clinical presentation and diagnostic test results of 32 adolescents with probable myopericarditis following mRNA COVID-19 vaccine administration.
*Other symptoms included shortness of breath, nausea, vomiting, chills, fatigue, headache, myalgia, sore throat, neck pain, diaphoresis and syncope.

Figure 3. Panel A: Phase sensitive inversion recovery sequence showing four-chamber slice with subepicardial late gadolinium enhancement involving basal, mid and distal anterolateral left ventricular wall segments**. Panel B:** Phase sensitive inversion recovery sequence showing short axis basal slice with subepicardial late gadolinium enhancement involving inferior and infero-lateral left ventricular wall segments.

Table 1. Characteristics of 32 adolescents with probable myopericarditis following mRNA COVID-19 vaccine administration.

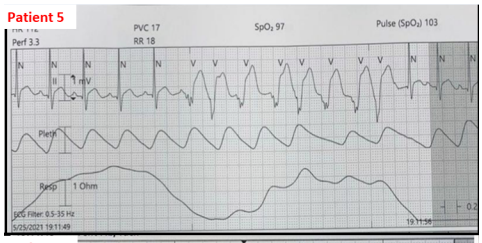
Patient	Age	Sex	Race	mRNA vaccine dose	Days from vaccination to symptoms	Symptoms	CRP (mg/dL) Normal: <0.3 mg/dL	Tn (ng/mL) Normal ≤ .04 ng/mL	ECG	ECHO	CMR	Rx	Hospital days and Clinical course
1.	15	M	C	2nd	2	Chest pain, fever, nausea, vomiting, shortness of breath	↑ (8.9)	↑ (24.6)	ST↑	LV Fx ↓ (LVEF 49%)	LGE+	Ibuprofen	5 (LV function normal on discharge)
2.	15	F	C	2nd	2	Chest pain	↑ (25.4)	↑ (41.9)	ST↑ and T wave inversion in lateral leads	NL LV Fx	LGE+, edema	Ibuprofen	3
3.	15	M	C	2nd	Few hours	Fatigue, chills, shortness of breath, chest pain, vomiting	↑ (23.5)	↑ (12.9)	T wave inversion in lateral leads, PVC's	NL LV Fx	LGE+, edema	Ibuprofen	3
4.	17	M	H	1st	20	Chest pain	ND	↑ (5.6)	Non-specific ST changes	NL LV FX	ND	Ibuprofen	Outpatient management only
5.	17	M	H	2nd	1	Chest pain	↑ (1.5)	↑ (11.3)	ST↑ NS VT	NL LV Fx	LGE+	Ibuprofen, IVIG	3
6.	17	M	H	2nd	4	Chest pain	ND	↑ (4.8)	ST↓	NL LV Fx	ND	Ibuprofen	2
7.	16	M	H	2nd	4	Chest pain	↑ (1.8)	↑ (4.5)	ST↑ PR↓	NL LV Fx	LGE+	Ibuprofen	3
8.	15	M	H	1st	3	Chest pain	↑ (2.8)	↑ (11.8)	Normal 2 episodes of NS VT	NL LV Fx	LGE+	None	3
9.	16	M	H	2nd	1	Chest pain	ND	↑ (2.42)	ST↑	NL LV Fx	ND	Ibuprofen	2
10.	12	M	C	2nd	4	Chest pain	ND	↑ (1.7)	ST↑	NL LV Fx	ND	Ibuprofen	Outpatient management only
11.	15	M	H	2nd	2	Chest pain	ND	↑ (5.1)	Normal	NL LV Fx	ND	Ibuprofen	2

12.	15	M	H	2nd	3	Chest pain	ND	↑ (23.5)	ST↑	NL LV Fx	ND	Ibuprofen	2
13.	17	M	C	2nd	1	Chest pain	ND	↑ (5.1)	ST↑	NL LV Fx	ND	Ibuprofen	1
14.	17	F	O	2nd	2	Chest pain	↑ (4.7)	↑ (24.7)	ST ↑	NL LV Fx, small PE	ND	Ibuprofen	4
15.	15	M	C	2nd	2	Chest pain	↑ (1.65)	↑ (11.6)	ST↑	NL LV Fx	ND	Ibuprofen	4
16.	14	M	C	2nd	2	Chest pain	↑ (7.8)	↑ (38.4)	ST↑	LV Fx ↓ (LV EF 52%)	ND	Ibuprofen	4
17.	15	M	C	2nd	1/2	Chest pain, shortness of breath	↑ (5.2)	↑ (8.47)	ST↑ PR↓	LV Fx ↓	ND	Ibuprofen	6
18.	15	M	C	2nd	2	Chest pain, headache, myalgias, chills	↑ (5.43)	↑ (29.2)	ST ↑ PR ↓	NL LV Fx	ND	Ibuprofen, then oral corticosteroids	3
19.	13	M	A	2nd	2	Chest pain, fatigue, sore throat	↑ (4.8)	↑ (24.4)	ST ↑ QT↑	LV Fx ↓ (LVEF 52%)	ND	Milrinone, ibuprofen, then oral corticosteroids	3
20.	15	M	C	2nd	3	Chest pain, malaise	ND	↑ (3.67)	Nonspecific T wave flattening	NL LV Fx	ND	Oral corticosteroids	3
21.	17	M	H	2nd	2	Chest pain, fever, chills	↑ (5.56)	↑ (2.1)	ST↑	NL LV Fx	LGE+, small PE	Ibuprofen	2
22.	14	M	A	2nd	2	Chest pain, shortness of breath, shoulder and neck pain	↑ (2.36)	↑ (1.1)	ST↑	NL LV Fx	LGE+	Ibuprofen	4
23.	14	M	O	2nd	2	Chest pain	↑ (4.25)	↑ (2.1)	ST↑	NL LV Fx	LGE+	Ibuprofen	2
24.	12	M	C	2nd	3	Chest pain, diaphoresis, tingling of fingers	↑ (.94)	↑ (1.1)	ST↑	NL LV Fx	LGE+	Ibuprofen	2
25.	17	M	H	2nd	4	Chest pain. myalgia headache	↑ (8.4)	↑ (3.6)	ST↑	NL LV Fx	LGE+, edema	Ibuprofen	3

26.	16	M	C	2nd	3	Chest pain fever headache	↑ (9.5)	↑ (5.4)	ST↑ NSVT	NL LV Fx	LGE+, Edema	Naproxen, enalapril, spironolactone	4
27.	16	F	AA	1st	5	Chest pain, syncope	(0.4)	↑ (1.2)	LBBB, junctional rhythm, first degree AV block, T wave inversion	LV Fx ↓ (LV EF 48%)	LGE+, edema, small PE	Lasix, Ibuprofen	5
28.	13	F	AA	2nd	2	Chest pain	↑ (4.4)	↑ (0.6)	Non-specific ST changes	NL LV Fx, small PE	LGE -, small PE	Ibuprofen	4
29.	16	M	C	2nd	2	Chest pain, fever	↑ (8.4)	↑ (18.5)	Normal	NL LV Fx	LGE+, edema	Enalapril, spironolactone	1
30.	15	M	H	2nd	2	Chest Pain	↑ (2.1)	↑ (13.1)	Normal, SVT 4 beats	NL LV FX	ND	Ibuprofen	5
31.	15	M	C	2nd	2	Chest pain, nausea, vomiting, tactile fever	↑ (26.2)	↑ (6.4)	Diffuse non-specific ST changes	NL LV Fx	LGE+	Ketorolac, IVIG, methylprednisolone, low dose aspirin	7
32.	16	M	AA	2nd	2	Fever, chest pain	NL	↑	ST ↑	NL LV Fx	ND	Ibuprofen	Outpatient management only

C, Caucasian; AA, African American; H, Hispanic; A, Asian; O, Others; ECG, Electrocardiogram; ECHO, Echocardiography; CMR, Cardiac magnetic resonance; M, Male; F, Female; ND: Not done; NL, Normal; LV, Left ventricle; Fx, Function; LGE, Late gadolinium enhancement; NS VT, Non-sustained ventricular tachycardia; SVT, Supraventricular tachycardia; Rx, Treatment; CRP, C-Reactive protein; Tn, Serum troponin concentration; PE, Pericardial effusion.

Patient 5



Patient 8